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Occupational Benzene Exposure and Lymphoma Risks

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In their recent meta-analysis, Vlaanderen et al. (2011) claimed to show evidence for associations between occupational benzene exposure and risks of multiple myeloma, acute lymphocytic leukemia, and chronic lymphocytic leukemia. However, one of the larger available studies, including 5,514 benzene-exposed UK workers (Sorahan et al. 2005), was excluded from this meta-analysis, apparently because the study had an elevated standardized mortality ratio (SMR) for secondary and unspecified cancers. On the basis of national mortality rates, we would have expected 7% of all cancer deaths in the UK study to have been in the unspecified category (e.g., carcinomatosis, mesothelioma with site unspecified); however, 9% of deaths were unspecified. Given the size of the study (2,430 deaths from all causes), this difference was statistically significant (Sorahan et al. 2005). Is it reasonable to conclude that a study with 93% of cancer deaths with site of cancer specified is informative but one with only 91% specified is not? I do not believe that it is. Vlaanderen et al. (2011) are of course free to come to a different conclusion, but any conclusion they reach must be implemented in an even-handed way. Some obvious questions then arise: *a*) How elevated did the SMR for unspecified cancers have to be for a study to be excluded from their meta-analysis? *b*) Were all the other studies assessed against this criterion? *c*) How many studies did not provide enough information for this criterion to be assessed? *d*) Why was this number not supplied by Vlaanderen et al. (2011)?

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Occupational Benzene Exposure and Lymphoma Risks: Vlaanderen et al. Respond

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We appreciate Sorahan's interest in our study (Vlaanderen et al. 2011). We first evaluated the article by Sorahan et al. (2005) for inclusion in our meta-analysis based on its analysis of cancer incidence, which is consistent with our stated preference for using incidence rather than mortality data when both were available (Vlaanderen et al. 2011). Because the authors themselves had expressed serious concerns with regard to the underascertainment of cancer registrations (incidence) (Sorahan et al. 2005), we decided not to include these data and instead considered their mortality analysis, which was included in the same article (Sorahan et al. 2005). We then decided to exclude their mortality data as well because of their "inability to identify the type of cancer for a number of cancer deaths" (Vlaanderen et al. 2011). A total of 9% of all cancer deaths were not identified by type by Sorahan et al. (2005), compared to 2–6% from the publications we considered for inclusion that provided such data (9 of 40 cohorts reviewed). We did not make this decision based on the SMR for this category, as Sorahan claimed in his letter. Inclusion of the mortality data from Sorahan et al. (2005) has a negligible impact on our results [Table 1 compared with Supplemental Material, Table 1 of our paper (http://dx.doi.org/10.1289/ehp.1002318)]

Table 1. Pooled risk estimates (and 95% confidence intervals) for AML and five lymphoma subtypes stratified by start of follow-up and AML significance level and including data from Sorahan et al. (2005).

Lymphoma subtype/ AML significance level[a]	No. of studies	No. of cases	Meta relative risk (all studies)	No. of studies	No. of cases	Meta risk ratio (start follow-up before 1970)	No. of studies	No. of cases	Meta risk ratio (start follow-up 1970 and later)
AML									
A–E (all studies)	*22*	*229*	1.69 (1.38–2.08)*	*13*	*131*	*1.47 (1.12–1.92)**	9	98	2.08 (1.59–2.72)
A–D	*22*	*229*	*1.69 (1.38–2.08)**	*13*	*131*	*1.47 (1.12–1.92)**	9	98	2.08 (1.59–2.72)
A–C	*17*	*204*	*1.87 (1.57–2.22)*	*9*	*112*	*1.72 (1.38–2.15)*	8	92	2.11 (1.61–2.77)
A–B	*12*	*144*	*2.15 (1.76–2.63)*	*6*	*76*	*1.99 (1.51–2.60)*	6	68	2.41 (1.77–3.29)
A	*10*	*120*	*2.38 (1.89–2.99)*	*5*	*63*	*2.13 (1.57–2.89)*	5	57	2.88 (1.95–3.99)
HL									
A–E (all studies)	*28*	*149*	*1.00 (0.84–1.18)*	*20*	*126*	*1.01 (0.84–1.23)*	8	23	0.91 (0.59–1.40)
A–D	*13*	*72*	*0.99 (0.78–1.27)*	*9*	*61*	*1.03 (0.79–1.35)*	4	11	0.83 (0.47–1.48)
A–C	*10*	*42*	*0.84 (0.61–1.16)*	*6*	*31*	*0.84 (0.57–1.24)*	4	11	0.83 (0.47–1.48)
A–B	*6*	*10*	*0.57 (0.30–1.10)*	*3*	*9*	*0.65 (0.31–1.38)*	3	*1*[b]	0.40 (0.11–1.44)
A	*5*	*10*	*0.61 (0.31–2.19)*	*3*	*9*	*0.65 (0.31–1.38)*	2	*1*[c]	0.46 (0.10–2.09)
NHL[d]									
A–E (all studies)	*34*	*662*	*1.00 (0.89–1.12)**	*23*	*467*	*0.93 (0.82–1.05)*	11	195	1.21 (0.94–1.55)*
A–D	*16*	*398*	*0.96 (0.81–1.14)*	*9*	*223*	*0.83 (0.68–1.01)*	7	175	1.18 (0.91–1.53)*
A–C	*14*	*359*	*0.98 (0.81–1.18)*	*7*	*184*	*0.83 (0.65–1.05)*	7	175	1.18 (0.91–1.53)*
A–B	*8*	*145*	*1.16 (0.85–1.57)*	*3*	*55*	*0.89 (0.62–1.27)*	5	90	1.38 (0.92–2.06)*
A	*7*	*116*	*1.10 (0.78–1.55)*	*3*	*55*	*0.89 (0.62–1.27)*	4	61	1.40 (0.79–2.51)*
MM									
A–E (all studies)	*27*	*290*	*1.11 (0.97–1.26)*	*17*	*210*	*1.06 (0.92–1.22)*	10	80	1.26 (0.92–1.71)
A–D	*15*	*166*	*1.13 (0.93–1.37)*	*8*	*111*	*1.06 (0.87–1.30)*	7	55	1.27 (0.81–2.00)*
A–C	*13*	*143*	*1.15 (0.91–1.44)*	*6*	*88*	*1.08 (0.86–1.34)*	7	55	1.27 (0.81–2.00)*
A–B	*8*	*75*	*1.40 (1.02–1.90)*	*3*	*35*	*1.20 (0.73–2.00)*	5	40	1.58 (1.03–2.44)
A	*7*	*62*	*1.42 (0.97–2.08)*	*3*	*35*	*1.20 (0.73–2.00)*	4	27	1.75 (0.94–3.26)
ALL									
A–E (all studies)	*18*	*47*	*1.41 (1.02–1.97)*	*11*	*30*	*1.27 (0.86–1.87)*	7	17	1.92 (1.00–3.67)
A–D	*18*	*47*	*1.41 (1.02–1.97)*	*11*	*30*	*1.27 (0.86–1.87)*	7	17	1.92 (1.00–3.67)
A–C	*12*	*29*	*1.36 (0.88–2.10)*	*6*	*15*	*1.04 (0.60–1.81)*	6	14	2.10 (1.04–4.25)
A–B	*8*	*16*	*1.59 (0.85–2.99)*	*3*	*5*	*0.98 (0.38–2.58)*	5	11	2.28 (0.99–5.26)
A	*6*	*12*	*1.52 (0.71–3.26)*	*2*	*3*	*0.88 (0.27–2.81)*	4	9	2.30 (0.84–6.29)
CLL									
A–E (all studies)	*19*	*116*	*1.16 (0.81–1.65)**	*12*	*74*	*0.91 (0.56–1.48)**	7	42	1.63 (1.09–2.44)
A–D	*19*	*116*	*1.16 (0.81–1.65)**	*12*	*74*	*0.91 (0.56–1.48)*	7	42	1.63 (1.09–2.44)
A–C	*14*	*98*	*1.20 (0.78–1.84)**	*8*	*60*	*0.91 (0.47–1.75)*	6	38	1.61 (1.00–2.59)
A–B	*9*	*62*	*1.37 (0.80–2.35)**	*5*	*43*	*1.13 (0.43–2.97)*	4	19	1.84 (1.12–3.02)
A	*7*	*50*	*1.36 (0.74–2.51)*	*4*	*41*	*1.40 (0.49–4.01)*	3	9	1.33 (0.64–2.76)

Abbreviations: ALL, acute lymphocytic leukemia; AML, acute myelogenous leukemia; CLL, chronic lymphocytic leukemia; HL, Hodgkin lymphoma; MM, multiple myeloma; NHL, non-Hodgkin lymphoma. Data presented here correspond to Supplemental Material, Table 1 from Vlaanderen et al. (2011; http://dx.doi.org/10.1289/ehp.1002318). Sorahan et al. (2005) was categorized as follow-up starting before 1970; AML significance level A [relative risk > 1 ($p < 0.1$)]; exposure assessment quality D (qualitative indication that benzene exposure had occurred). No observed cases were reported for ALL by Sorahan et al. We therefore calculated continuity-corrected relative risks (observed and expected number of cases + 1) and estimated associated 95% confidence intervals with mid-P exact. Values that are different from those in the original analyses are in italic type.
[a]AML significance level categories: A, AML risk estimate > 1 ($p < 0.1$); B, AML risk estimate > 1 ($p < 0.2$); C, AML risk estimate > 1 ($p > 0.2$); D, AML risk estimate reported; E, AML risk estimate not reported. [b]Two of three studies reported null cases (continuity correction was applied in the meta-analysis). [c]One of two studies reported null cases (continuity correction was applied in the meta-analysis). [d]NHL or lymphosarcoma/reticulosarcoma (preferred NHL if the study reported both). *$p < 0.1$ for between-study heterogeneity.

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Vlaanderen J, Lan Q, Kromhout H, Rothman N, Vermeulen R. 2011. Occupational benzene exposures and the risk of lymphoma subtypes: a meta-analysis of cohort studies incorporating three study quality dimensions. Environ Health Perspect 119:159–167.

and does not alter our conclusion that this meta-analysis provides support for an association between occupational exposure to benzene and increased risk of multiple myeloma, acute lymphocytic leukemia, and chronic lymphocytic leukemia (Vlaanderen et al. 2011).

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In Favor of Controlling Proven, but Not Probable, Causes of Cancer

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We wish to compliment and complement the editorial by Landrigan et al. (2011) who *inter alia* synthesized the "Asturias Declaration" during the "International Conference on Environmental and Occupational Determinants of Cancer: Interventions for Primary Prevention" [World Health Organization (WHO) 2011]. Although the authors list recommendations that are certainly commendable, we strongly disagree with the inclusion of "probable" in the suggestion that "the WHO should develop a global framework for control of environmental and occupational carcinogens that concentrates on the exposures identified by IARC [International Agency for Research on Cancer] as proven or probable causes of human cancer."

Indeed, we would strongly suggest the need to focus on the causes of human cancer that have been identified by IARC as proven, but not on "probable" causes [59 agents have been classified by IARC as group 2A, i.e., probably carcinogenic to humans (IARC 2011)] to then direct premature prevention efforts on the latter. Soberingly, IARC's diligent evaluation process of what can and what cannot cause cancer in humans would be blurred when equating group 1 (proven carcinogen) classifications with group 2A classifications, as recommended in the Asturias Declaration. A group 2A classification is not necessarily part of a one-way street to a group 1 verdict.

To provide a recent, empirical example, shift-work that involves circadian disruption was classified as a probable human carcinogen (Straif et al. 2007). Importantly, though, as long as causality is not established, we should clearly be deterred from activities that are not driven by data. Moreover, means for primary prevention are elusive (Erren et al. 2009): Shift-work is unavoidable in our 24/7 societies, and it is impossible with today's state of knowledge to identify workers who are robust to shift-work conditions and to dissuade others who may be susceptible to the effects of circadian disruption or chronodisruption (Erren et al. 2008; Erren and Reiter 2008). An IARC classification of "probable" human carcinogen, which implies uncertainty and the possibility that future research may exonerate the "culprit in question," is certainly not an appropriate yardstick to guide valuable and limited resources. Instead, we should invest in controlling established carcinogens such as asbestos and smoking.

Overall, when Richard Nixon declared the war on cancer on 23 December 1971, he remarked, "I hope in the years ahead that we may look back on this day and this action as being the most significant action taken during this administration" (Nixon 1971b). That initiative certainly is not—not only because of the Watergate scandal but, importantly, because of the highly ambitious goal "to find a cure for cancer" (Nixon 1971a). Lacking insights into how to cure cancer in the majority of cases, our objective for now—and presumably for many years to come—should be improved primary prevention of environmentally and occupationally caused cancers. Clearly, although progress in prevention is necessary and feasible, it is imperative to identify realistic and defensible goals and strategies. To this end, a sensible recommendation for strategy would be that "a new global policy framework for environmental cancer" (Landrigan et al. 2011) should focus on established carcinogens such as asbestos, "smoking, overweight, and inactivity" (Willett et al. 2011)—but not on probable culprits.

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In Favor of Controlling Proven, but Not Probable, Causes of Cancer: Landrigan et al. Respond

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We thank Erren et al. for their positive comments about our editorial on environmental and occupational causes of cancer (Landrigan et al. 2011). In particular, we acknowledge their support of our central thesis, expressed in the Declaration of Asturias [World Health Organization (WHO) 2011], that control of the toxic chemical causes of cancer must be a core component of global cancer control programs, equal in importance with efforts to understand and control